REMARKS

Amendments of December 1, 2003: Removal of the Rejections under 35USC§112, second paragraph: Removal of the prior indefinite rejections is acknowledged.

Amendment of the Specification: The specification stands amended at page 51 to incorporate material previously incorporated by reference, i.e., Examples 1-6 of Applicant's patent application 09/547,506 (now issued as U.S. 6,548,484 B1). Examples 1-6 in 09/547,506 are now renumbered for consistency as Examples 1-1 through 1-6. Replacement Pages 51 and 51A-D are transmitted herewith. The amendment introduces no new matter.

Amendment of the Claims:

After canceling Claims 5, 17, 18 and 20, Claims 41, 4, 10-16, 19 and 21-40 are pending.

In the interest of advancing prosecution for certain methods, Applicant has directed the present claims, e.g. Claim 4, to CNS-acting amine and amide prodrugs having a "bridge" and "A"-ring structure consistent with Claim 41 (Amended). Appendix A, following the Remarks section, relates the chemical structures of the compounds in Claim 4 and is provided as a courtesy to the Examiner. (Chemical structures were copied from the National Library of Medicine website at http://chem.sis.nlm.nih.gov/chemidplus.)

Claim 41 stands amended to incorporate dependent Claims 17, 18 and 20 and to cite additional method steps for determining blood-brain barrier penetration of the reaction product.

Claims 10 and 11 stand amended to correct obvious errors. The Examiner is thanked for her thorough proof reading.

Claim 21 stands amended to correct the typographical error by adding a period.

Claim 23 stands amended e.g. to change dependency.

Rejection of Claims 41, 4-5 and 10-40 Under 35 U.S.C. § 112, second paragraph

To recite the presently claimed invention with more particularity, the current amendments (a) incorporate Claims 17, 18, 20 and TABLE A into Claim 41; (b) define with more particularity the substitution in the N-alkyl bridge, i.e., Claim 41 (Amended); (c) identify the CNS acting prodrugs of TABLE A, i.e., Claim 4 (Amended); and, (d) recite additional method steps for determining

improved blood brain barrier penetrability of the reaction product, i.e., Claim 41 (Amended). Support for the measuring blood brain barrier penetrability may be found e.g. in the specification at page 23, last paragraph and page 24, first paragraph.

Amendments to Claim 10 and Claim 11 correct errors and antecedent basis. Support for the amendments may be found at page 36, lines 5-12 of the specification, i.e., defining Ring 1; and, page 40, lines 11-16, i.e., defining aryl with representative examples including pyridyl, pyrimidinyl, thiadiazinyl and pyridazinyl.

Amendments to Claim 23 correct improper multiple selection.

In view of the amendments, removal of the rejections is respectfully requested.

Rejection of Claims 41, 4-5 and 10-40 Under 35 U.S.C. § 103(a)

Claims 41, 4-5 and 10-40 stand rejected under 35 USC § 103(a) as unpatentable over Likhoshersfov et al. in view of Mizuma et al., Takata et al. and Vannucci et al.

The Office has argued that:

> "*Likhoshersfov et al. discloses the incorporation of carbohydrate residues into active compounds such as dopamine to form dopamine glycoconjugates, the instant elected species (see abstract). Likhoshersfov et al. does not expressly disclose the employment of the incorporation of carbohydrate residues into active compounds (active drugs) such as dopamine glycoconjugates in a composition and a method for improving the aqueous solubility and blood brain barrier penetrability of a drug.*" (the Paper mailing date February 26, 2004; page 4, lines 18-24)

That "*Likhoshersfov et al. does not expressly disclose the employment of the incorporation of carbohydrate residues into active compounds (active drugs) such as dopamine glycoconjugates in a composition and a method for improving the aqueous solubility and blood brain barrier penetrability of a drug.*", is the method of the claimed invention. As the Examiner has properly identified, the instant invention is " *a method for improving the aqueous solubility and blood brain barrier penetrability of a drug*". Respectfully, Applicant does not believe that methods for simultaneously improving aqueous solubility and blood brain barrier penetrability are motivated nor guidance provide to justify expectation of success in any documents relied upon in making the rejection under 35 USC §103(a). In particular, as the Examiner has appropriately noted that Likhoshersfov et al. does not disclose nor motivate methods for improved blood brain barrier penetrability or improved aqueous solubility or motivation for achieving same, i.e., the Claimed Invention. Cognitive recognition of methods that may be useful for improving blood brain barrier

penetrability of CNS acting prodrugs cannot occur if one skilled in the art is not provided guidance and in regard to desirable chemical properties and synthesis methods for enabling blood brain barrier penetration, Likhoshersfov et al. is moot. In regard to chemical structural requirements that must be met for transport at the blood brain barrier by GLUT1, Likhoshersfov et al. is moot. In regard to chemical structural requirements for preserving receptor ligand binding activity of active compounds, Likhoshersfov et al. is moot. In regard to methods and steps for determining that one has achieved successful blood-brain barrier penetration, Likhoshersfov et al. is moot. Similarly, the guidance lacking in Likhoshersfov et al. is not provided in any of the Mizuma et al., Takata et al. or Vannucci et al. documents that are relied upon in forming the basis for the rejections under 35 USC § 103(a), in fact the words "drug", "drug delivery", "active compound" or "pharmaceutical compound" do not appear in any of the references relied upon, i.e., as set forth in greater detail below. Mizuma et al. 72 (or 73) are defectively as references useful against blood brain barrier transport since intestinal sugar co-transporters, i.e., SGLT (Na^+ dependent glucose transporters), are not functionally or structurally related to GLUT (facilitative glucose transporters). Obviousness must be certain; references must be enabling; motivation must be provided; guidance must be certain; and, with expectation of success, i.e., as detailed further below.

Contrary to the position taken by the Office, the references relied upon show definite limitations in the art and identify the cautious limitations placed on the interpretation of the results by the authors of same. Motivation and expectation of success are lacking in the references relied upon. Instead, the art of relied upon serves to highlight the inherent limitations and unpredictability in the art, i.e., as follows: namely,

(i) Mizuma et al., ID No. 72 relates to intestinal absorption of glucose compounds as studied in the everted sac of the rat small intestine with motivation and uncertainty clearly identified, e.g.,

> "*A number of drugs which are pharmacologically active are poorly absorbed from the intestine and it would be valuable to find ways of overcoming this poor absorption." (page 2037, first line of the introduction); and,*
> *"Further studies are required to determine the extent of the improvement of intestinal absorption by conjugation of glucose or galactose to non- or poorly absorbable drugs.*" (page 2039, last line of the communication).

Technical limitations clearly warranted the cautious interpretation of the results by the authors, i.e., advisedly to one of skill in the art since in the reported experiments had the following

limitations: namely, (a) attempts to measure intestinal absorption, (i.e., not the blood brain barrier penetrability of the instant invention), were made *ex vivo* in tissue having no blood supply (page 2037, left column, last paragraph); (b) by applying non-pharmacological concentrations of test compounds, i.e., 250μM (Fig. 1 and Fig. 2, page 2038) and up to 10mM (Table 1, page 2038); (c) with clearance of non-transported mannose and glucuronic acid containing sugars being observed (page 2039, lines 6-19), i.e., suggesting possible leaks in the intestinal sacs used in the experiments; and, (d) with the test compounds (p-nitrophenyl and β-naphthyl glycosides, page 2037, Materials and Methods, first paragraph) not comprising drugs or CNS acting prodrugs, (i.e., not the compositions of the methods of the claimed invention).

As the Examiner has properly noticed, Mizuma et al. ID No. 72 does not disclose nor motivate steps for achieving blood brain barrier penetrability or improved aqueous solubility for CNS acting prodrugs. Similarly, Mizuma et al. 72 (and 73) does not disclose nor motivate methods for synthesizing compounds having chemical structures transportable by GLUT at the blood brain barrier. Distancing any possible motivation (attributed by the Office) in Mizuma et al. from the instant invention, sodium-dependent glucose co-transporters (SGLT) are the primary transporters in the small intestine (as set forth further below in regard to Takata et al. ID No. 96). SGLT are not related structurally or functionally to the GLUT family of glucose transporters operative at the blood brain barrier, (i.e., the instant invention). GLUT transporters, unlike SGLT, do not function as bidirectional co-transporters of sodium and glucose and are not driven by Na^+ gradients in cells. Thus, even if one of skilled in the art at the time had been motivated to test the compounds of Likhoshersfov et al. in the methods of Mizuma et al. they would not have arrived at results which would have motivated yet further testing of blood brain barrier penetrability, i.e., the claimed invention. Obviousness must be certain and with expectation of success. The mere motivation to conduct experimentation is not appropriate basis for a holding of obviousness.

(ii) Mizuma et al., ID No. 73, (using the same everted intestinal sac study system with the same deficiencies as discussed above in regard to ID No. 72), motivates similar caution as follows: namely,

> *"Active absorption in the intestine and metabolism of the β- and α-anomers of the glucoside and galactoside of p-nitrophenol (p-NP) were studied to find a more suitable prodrug for poorly absorbed drugs." (page 1520, first line of the Abstract); and,*
> *"Since these studies are limited to the p-NP glucoside and galactoside, further investigations into other compounds and drugs conjugated with glucose and galactose are necessary to obtain insight into sugar-containing prodrugs for improved drug absorption."* (page 1523, last line of the communication).

Motivating "*further investigations into other compounds*" or conjugation for possible improved drug absorption in the intestine does not motivate or render expectation of success for the instant blood brain barrier method (Claim 41, Amended). Motivation to experiment is not sufficient basis for a holding of obviousness absent expectation of success. Expectation of success in intestinal transport does not translate to blood brain barrier penetrability, i.e., for at least the reasons set forth above in regard to Mizuma et al. 72. Further, expectation of success in intestine is even lacking in Mizuma et al. 73 (or 73) for at least the following reasons: namely, as noted above in regard to ID No. 72, one of ordinary skill would appreciate technical limitations in Mizuma ID No. 73 and the cautious interpretation of the authors: for example, the findings are based upon: (a) *ex vivo* measurements taken without blood supply in an everted rat intestinal sac; (b) where clearance of non-drug compounds (p-nitropheyl glucopyranosides) applied at 250μM was measured using HPLC and fluorimetry; and (c) where, despite the known inability of α-anomers to be transported, the authors report that the tested (possibly rearranged) α-anomers were cleared from the mucosal side to the serosal side of the sac (Abstract, page 1520). The author's cautiously stated interpretations of their data (above), thus, mirror the inherent limitations in their study system and data.

Vannucci et al., (ID No. 99, below), teaches GLUT1 in brain. Similarly, Takata et al. (ID No. 96; relied upon in forming basis for the rejections) teaches as follows: namely,

> *"Although further studies are needed, GLUT1 is clearly the major transporter in the blood-brain barrier, and the contribution of GLUT3 to the transfer of glucose across the barrier is probably minimal, if any (Maher et al., 1993, 1994; Vannucci 1994)"* (page 12, lines 31-35).

Thus, the references relied upon teach that one of ordinary skill at the time would recognized that sugar transport by SGLT in intestine did not relate to GLUT1 in brain, i.e. intestinal transport of sugars experimentally provided neither motivation nor expectation of success in regard to even sugar transport at the blood brain barrier. The arguments are fatally flawed.

Applicant's Agent has conducted a thorough and futile search of the text of Mizuma et al. 72 and 73 for any of the following words: namely, "active compound", "active drug", "pharmaceutical compound", "drug", "prodrug", "glycoconjugate-drug", "glycoconjugate", "drug delivery", "aqueous solubility" or "improved blood-brain barrier penetrability", i.e., the claimed invention. The only compound, other than sugars and their metabolites, that was identified in this detailed search which might be considered "active" is phloridzin, which was used as a metabolic inhibitor of glucose transport in certain experiments (e.g. Ref. ID No. 73, page 1522, left column, lines 5-14).

Applicant believes motivation is clearly lacking in Mizuma et al. 72 (or 73) for doing what Applicant has done, i.e., for making the jump from intestinal sugar transport mediated by sodium dependent transporters (SGLT1), to blood brain barrier penetrability mediated by GLUT1; or, for making the jump from simple glucose, galactose and maltose molecules to CNS active prodrug compounds (the claimed invention). Moreover, given that Mizuma et al. 72 and 73 are defective as a blood-brain barrier references, there appears no basis to support attributed motivation or expectation of success, i.e.,

> *"One having ordinary skill in the art at the time the invention was made would have been motivated to employ conjugates of carbohydrate residues and active compounds (active drugs) such as dopamine glycoconjugates in the compositions and a method for improving the aqueous solubility and blood brain barrier penetrability of a drug, since active compounds (active drugs) such as dopamine glycoconjugates are known according to Likhoshersfov et al.. Moreover, the teachings of Mizuma et al., Takata et al. and Vannucci et al. have provided the motivation to make conjugates of carbohydrate residues and active drug compounds herein since sugar-conjugated drugs such as glucose-conjugated compounds provide these compounds (drugs) with a new route by the way of the glucose transport carrier for better absorption in intestine and improving the poorly absorbable drugs, and also enhancing the blood brain barrier penetrability of a drug."* (the Action, page 5, 2nd paragraph)

Hindsight reconstruction using Applicant's specification as a guide is also not an appropriate basis for forming a prime facie case of obviousness under 35 USC §103(a).

(iii) Takata, ID No. 96, reviews reports relating to GLUT1, a tissue glucose transporter that is hypothesized by the authors to be involved in transport of glucose at the blood brain barrier, e.g. "*We propose that GLUT1 is the glucose transporter isoform of blood-tissue barriers* (Takata et al., 1990 a,b)." (page 37, VI Concluding Remarks, line 2-3). Published under the title "Transport of Glucose Across the Blood-Tissue Barriers" Takata interpret the prior art as follows: namely,

> *"Specific transport mechanisms across such blood-tissue barriers must exist for a number of substances. In this chapter, we focus on the cellular and molecular basis for the transport of glucose across the blood-tissue barriers."* (page 2, lines 9-12); and,
> *"An abundance of GLUT1 at the critical plasma membranes of cells of the blood-tissue barrier ensures a sufficient supply of glucose to cells isolated from the general circulation. Among the six isoforms, GLUT1 appears to serve as the main glucose transporter for the blood-tissue barriers. Transport of glucose via GLUT1 is little affected by the regulatory mechanism under physiological conditions, which makes a marked contrast to the transport via GLUT2 or GLUT4. Such steady characteristics of GLUT1, together with its high affinity to glucose, may be ideal as a glucose transport machinery in the blood-tissue barriers in which a constant and stable supply of glucose is critical. Further analysis of the glucose transport system across the blood-tissue barriers, along with comparative and developmental studies, will lead to a more detailed characterization of these barriers."* (page 37, Concluding Remarks, lines 7-19).

Applicant's Agent has conducted a thorough and futile search of the text of Takata et al. for any of the following words: namely, "active compound", "active drug", "pharmaceutical compound", "drug", "prodrug", "glycoconjugate-drug", "glycoconjugate", "drug delivery", "aqueous solubility" or "improved blood-brain barrier penetrability", i.e., the claimed invention. In the entire 37 pages of text only 3 compounds (other than glucose and tracer proteins) are identified that might be considered "active": i.e.,

> cytochalasin B (i.e., identified 3-times on page16, lines 9,15 and 16; 3-times on page 26, lines 35,36 and 39; and once on page 27, line 10);
> ploretin (i.e., identified once on page 26, line 35); and,
> dexamethasone is identified (i.e., one time at page 36, lines 23-28).

Cytochalsin B and ploretin are both cited, not in the context of drug delivery, but instead for their ability to disrupt glucose uptake because of binding to cellular plasma membrane microtubular elements associated with GLUT1. Similarly, dexamethasone is identified, not for blood-brain barrier delivery, but instead for its ability to change the expression of GLUT1 in rat tumor microvessels.

In the absence of any verbal mention what-so-ever, it is difficult to posit that Takata et al. motivates: (a) delivery of an "active compound" or an "(active drug)"; or, (b) drug delivery; or, (c) using any glycoconjugated drug compounds; or, (d) using compounds such as those of Likhoshersfov et al. in a manner asserted by the Office, i.e.,

> *"Both Takata et al. and Vannucci et al. teach the transport of glucose across blood-tissue barriers such as blood-brain barrier (see abstracts). It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ conjugates of carbohydrate residues and active compounds (active drugs) such as dopamine glycoconjugates in a composition and a method for improving the aqueous solubility and blood brain barrier penetrability of a drug."* (page 5, lines 4-10).

Further, Takata et al. relates to transport of glucose which is an abundant small molecule essential for the brain with disclosure also of metabolic requirements and rapid transport across blood-tissue barriers. The latter disclosure can equally well be viewed as teaching away from that which Applicant has done, i.e., one skilled in the art recognizing that abundant glucose molecules and rapid transport at the blood-brain barrier would be led to believe that these molecules would easily and effectively compete any desired transport of a glycoconjugate drug. Similarly, the high transporter affinity of GLUT for glucose, as disclosed in Takata et al., could be viewed as teaching away, i.e., by suggesting to one of skill the low likelihood that a structurally related compound would be able to compete with molecular glucose for transport. Further, those of skill would certainly recognize from the teaching of Takata et al. that any prodrug having a high binding affinity for a GLUT1 transporter could interfere with the normal transport of glucose into the brain, i.e., posing a significant risk of toxicity. Thus, for at least the preceding three reasons, Takata et al. may equally well be viewed as teaching away from that which Applicant has done, i.e., a secondary indicia of patentability overcoming obviousness.

Guidance and motivation is lacking in Takata et al., Mizuma et al. and Likhoshersfov et al. for that which Applicant has done. It is believed that Takata et al., properly read, relates to metabolic transport of sugars at blood-tissue barriers and not to organic synthesis methods for achieving improved blood brain barrier penetrability and aqueous solubility for a CNS acting prodrug. Takata et al. does not solve the motivation and guidance deficiencies noted above in Likhoshersfov et al. or the defects in Mizuma et al. 72,73.

(iv) Vannucci et al., ID No. 99, relate that investigation was directed toward answering the following question: namely,

> "*In normal adult rat over a broad range of circulating glucose concentrations, the levels of glucose transporter proteins are sufficient to insure an adequate supply of glucose to meet metabolic demand. The question arises as to whether or not this system for the delivery of substrate to brain is responsive to alterations in levels of either substrate supply or glucose metabolic demand. To address this question, we have investigated several different paradigms in which metabolic demand is altered chronically. What follows represents a compilation of previously published studies [for review, see Vannucci et al., 1997b], as well as recent novel findings.*" (page 370, left column, lines 1-12); and,
>
> "*The objective of this study was to address the potential relationship between rates of cerebral glucose utilization and the expression of the major glucose transporters in brain, GLUT1 and GLUT3. We have described several diverse paradigms in which we have been able to document just such parallel relationships.*

During normal post-natal development, increases in $rCMR_{glc}$ correspond to the relative maturity of the brain region, and are mirrored by increases in GLUT3. In contrast, decreases in $rCMR_{glc}$ in brains of patients with AD are reflected in decreases in both GLUT1 (BBB) and GLUT3. Furthermore, the decrease in GLUT3 is greater than can be accounted for by neuronal loss, suggesting a potential etiological significance in this neurodegenerative disease."

Like Takata et al. (discussed above), a thorough futile search was conducted by Applicant's Agent in the text of Vannucci et al. for any of the following words: namely, "active compound", "active drug", "pharmaceutical compound", "drug", "prodrug", "glycoconjugate-drug", "glycoconjugate", "drug delivery", "aqueous solubility" or "improved blood-brain barrier penetrability", i.e., the claimed invention. In the entire 10 pages of text only 2 compound (other than glucose and proteins) are identified that might be considered "active", (APV and NMDA, below), and none that could be considered drugs in the following context: namely,

"*Stimulation by NMDA resulted in 120% increase in transporter activity and a 45% increase in GLUT3 expression. Increasing potassium levels to 15mM resulted in a 33% increase in transport activity and a corresponding 50% increase in GLUT3, which could be augmented by the inclusion of NMDA. The effects of NMDA could be blocked by the addition of the antagonist APV (2-amino-5-phosphonopentanoic acid).*" (page 375, right column, bottom of the page, lines 2-9).

In the absence of any verbal mention what-so-ever, it is difficult to posit that Vannucci et al. motivates: (a) delivery of an "active compound" or an "(active drug)"; or, (b) drug delivery; or, (c) using any glycoconjugated drug compounds; or, (d) using compounds such as those of Likhoshersfov et al. in a manner asserted by the Office, i.e., as recited above in regard to Takata et al.

Further, the Office has asserted that both Takata et al. and Vannucci et al. "*teach transport of glucose across the blood-tissue barriers such as blood-brain barrier*". However, this selective recital ignores disclosure in Vannucci et al. that changes in transporter activity accompany metabolic changes, e.g. as follows in the Abstract (relied upon in forming basis for the rejection): namely,

"Glucose is the principle energy source for mammalian brain. Delivery of glucose from the blood to the brain requires its transport across the endothelial cells of the blood-brain barrier and across the plasma membranes of neurons and glia, which is mediated by the facilitative glucose transporter proteins. The two primary glucose transporter isoforms which function in cerebral glucose metabolism are GLUT1 and GLUT3. GLUT1 is the primary transporter in the blood-brain barrier, choroids plexus, ependyma, and glia; GLUT3 is the neuronal glucose transporter. The levels of expression of both transporters are regulated in concert with metabolic demand and regional rates of cerebral glucose utilization. We present several experimental paradigms in which alterations in energetic demand and/or substrate supply affect glucose transporter expression. These include normal cerebral development in the rat, Alzheimer's disease, neuronal differentiation in vitro, and dehydration in the rat." (Abstract, page 369, full text).

Assuming in argumentum the position of the Office, one of skill in the art wishing to assure uniform delivery of pharmaceutical drugs would surely be sorely discouraged by the teachings of Vannucci et al., i.e., the disclosure that metabolic and disease-related changes in expression of GLUT isoforms may render delivery non-predictable. Thus, like Takata et al., Vannucci et al. might be considered equally to teach away from that which Applicant has done. The deficiencies in Likhoshersfov et al., Mizuma et al. and Takata et al. are not cured by Vannucci et al.

Regarding the response of the Office to Applicant's remarks of December 3, 2003, i.e., page 6 of the Action, lines 3-22 and page 7, lines 1-11:

1. Applicant's remarks were directed toward the adequacy of Likhoshersfov et al. in motivating the method of the claimed invention with expectation of success, i.e., adequacy as an enabling disclosure given that the structure disclosed in Likhoshersfov et al. is morpholino and not dopamine; and, that dopamine is merely mentioned, not structurally disclosed. Since the Office has not previously chosen to reject the Specification, it is assumed that the disclosure is adequate under the statutes such that one of ordinary skill may practice the invention.

Respectfully, that "knowledge is power" is attributed to De Haeresibus in 1605 (Bartlett's Quotations, 16th Edition, 1992). What Applicant has succeeded in doing was not anticipated or obvious until it was done. Knowing now that glycosyl-drugs can effectively compete with glucose for entry into the brain and that the product compounds of the invention can survive transit to exert biological effects in the brain is key to designing future new generations of pharmaceutical compounds. A key caveat in international patent law is that is exchange for disclosing major new advances benefiting humanity, an inventor is rewarded through grant of rights to make, use and sell. Applicant (now deceased) will no longer benefit from all that the future will hold.

2. For avoidance of any further doubt, Applicant submits by way of a Supplemental Information Disclosure the recently published peer reviewed article of Jiang et al. (ID No. 107, below; transmitted herewith) in the April issue of Clinical Neuropharmacology originating from Baylor College of Medicine and describing observations; also presented at the American Association of Neurology meeting in San Francisco in Spring 2004 in an abstract selected as #1 in a special

poster session to highlight new advances at the opening reception of the meeting. Jiang et al. relates to: "*Further, biological activities, chemical stability and side effects and possible toxicity resulting from the instant resultant compounds resulting from the instant resultant compounds would also be in question.*" (the Action, page 6, lines 18-20). In this case, Jiang et al. disclose: (a) anti-Parkinson's activity of the elected species in three different mouse animal models; (b) *in vivo* chemical stability, i.e., the test involved intraperitoneal injection requiring stability to cross the peritoneal lining, survive first pass liver clearance, survive in blood to reach the blood-brain barrier intact (since dopamine-non-conjugated does not pass the blood brain barrier) then delivery across the blood-brain barrier in a therapeutically active form; (c) lack of observed side effects *in vitro* (cell cultures studies and receptor binding) and *in vivo* (direct injection into rat brain); and, (d) relative lack of toxicity (see Discussion section for data relating to dose-ranging toxicology trials).

Information Disclosure Statement:

Jiang et al. 2004, ID No. 107, co-authored by Applicant with investigators at Baylor College of Medicine, the University of Toronto and International Medical Innovations (Birmingham, AL), discloses biological properties of CNS acting prodrugs IPX-750 (amine) and IPX-760 (amide), which are glycosyl-dopamine compounds, (the elected species), produced according to methods of the instant invention. The report in April 2004 issue of the journal "Clinical Neuropharmacology" discloses dopaminergic receptor binding, cAMP activation and efficacy in three different animal models of Parkinson's disease.

Concluding Remarks

Obviousness must be certain. Obvious to try is not an acceptable standard, i.e., motivation and guidance are required. Expectation of success is required. References must be enabling. Picking and choosing is not appropriate in forming a prima facie case of obviousness. Reconstructing the prior art using Applicant's specification as a guide is not appropriate.

Briefly, as cited also in the Response of December 3, 2003:

The Federal Circuit *In re O'Farrell* examined a prior publication containing a written prophetic suggestion and provided the following instructions on predictability and apparent obviousness (emphasis added):

> "Obviousness does not require absolute predictability of success. Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice. There is always at least a possibility of unexpected results, that would then provide an objective basis for showing that the invention, although apparently obvious, was in law nonobvious..." In re O'Farrell, 853 f.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988).

In re Eli Lilly & Co. the Federal Circuit instructed:

> "An 'obvious-to-try' situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result..." In re Eli Lilly & Co., 942 F.2d 943, 14 USPQ2d 1056 (Fed. Cir. 1990).

In re. Epstein, the Federal Circuit instructed that printed publications

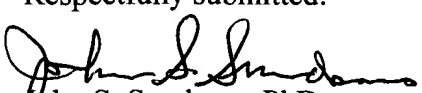
> "...must be enabling, thus placing the alleged disclosed matter in the possession of the public." In re. Epstein, 32 F.3d 1559, 31 USPQ2d 1817 (Fed. Cir. 1994)

See also Beckman Instruments, Inc. v. LKB Produkter AB, 892 F.2d 1547, 13 USPQ2d 1301 (Fed. Cir. 1989):

> "References relied upon to support a rejection for obviousness must provide an enabling disclosure. That is to say, they must put the claimed invention in the possession of the public."

In light of the amendments to the claims and remarks, removal of the rejections under 35 U.S.C. § 112 and 35 U.S.C. § 103 is respectfully requested. If any issues remain which can be expeditiously addressed in teleconference, the Examiner is urged to contact Applicant's agent at 760-806-3385 (office) or 615-423-3850 (mobile).

Respectfully submitted:



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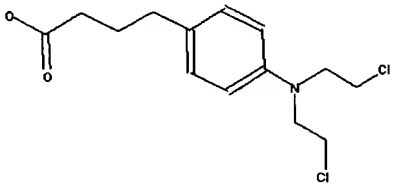
APPENDIX A

CHEMICAL STRUCTURES

(http://chem.sis.nlm.nih.gov/chemidplus/)

- **ANTINEOPLASTIC AGENTS**



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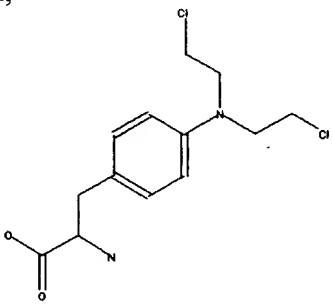

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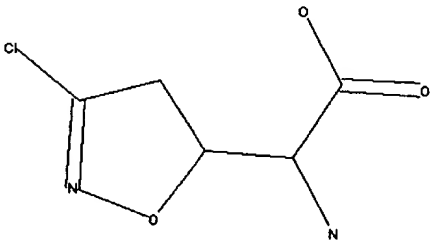

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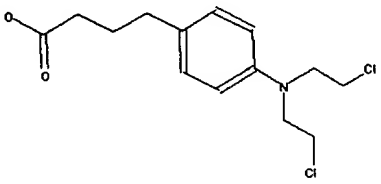
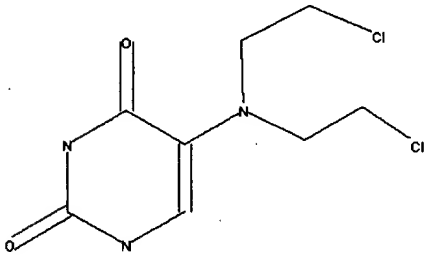
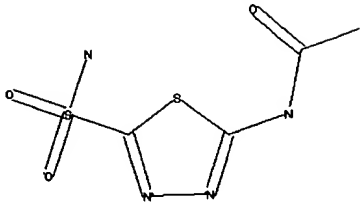


chlorambucil,



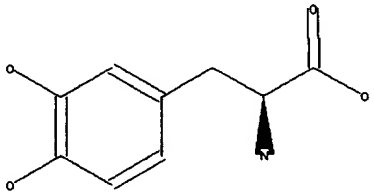
uracil mustard,

- **CARBONIC ANHYDRASE INHIBITORS**

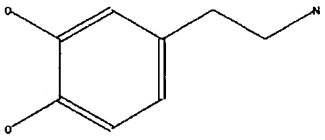


acetazolamide,

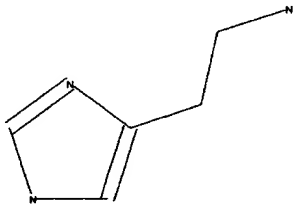
- **CATECHOLAMINES AND DOPAMINERGIC AGENTS**



L-DOPA,

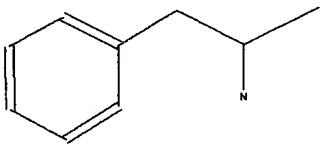


Dopamine,

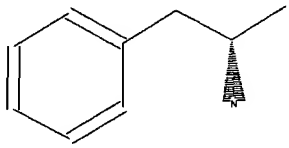


histamine,

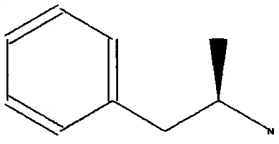
- **STIMULANTS**



amphetamine,



dextroamphetamine,



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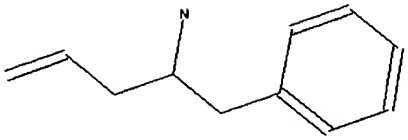
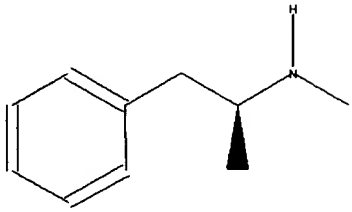
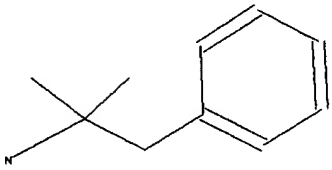


aletamine,

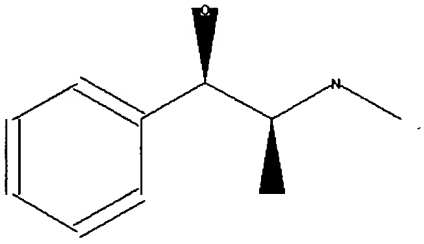


methamphetamine,

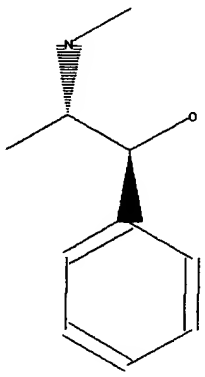


phentermine,

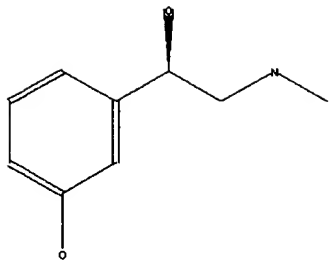
- **SYMPATOMIMETIC AMINES AND DECONGESTANTS**



ephedrine,

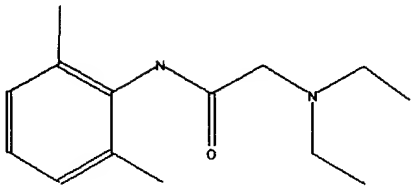


pseudoephedrine,



phenylephrine

- **ANAESTHETICS**



lidocaine

al., 1999; Shimada et al., 1991; Kilty et al., 1991; Giros et al., 1991; Vandenbergh, et al., 1992), sequences are reported (e.g., see U.S. Patent Serial No. 5,756,307) and homozygous and knock-out mice (e.g., see Jaber et al., 1999; reviewed in Gainetdinov et al., 1999) and cell lines (e.g. 1RB3AN27 dopamine neurons, see Clarkson et al., 1999; HEK 293 stably transfected cells, see Storch et al.; PC12 stably transfected cells, see Melikian et al., 1999; in MDCK stably transfected cells, see Wu et al., 1999) have been prepared. Other *in vitro* assays for assessing DAT transportability of a test compound include ligand-binding studies conducted e.g., with rat brain slices or rat caudate putamen membrane preparations.

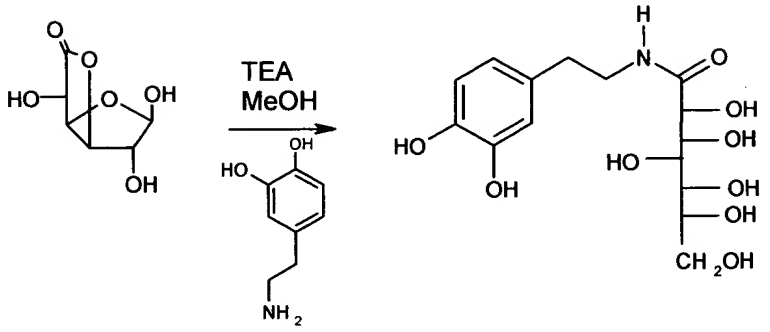
MPTP-Treated Mice: Progressive decreased expression of dopamine receptors and dopamine transporters accompanies treatments of mice with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; e.g. see Kilbourn et al., 2000), i.e., a similar pattern of changes to those observed in early onset Parkinson's disease by imaging (e.g., see Verhoeff, 1999). While certain of the neurophysiologic attributes of MPTP-treated mice may not mirror Parkinsonism, this animal model is widely used to evaluate the potential effects of test compounds in treatments for Parkinson's disease.

Additional disclosure of the N-linked glycosyl prodrug pharmaceutical compositions is contained within Applicant's copending U.S. Patent Application Serial No. 09/547,506 (now U.S. Patent Serial No. 6,548,484 B1), incorporated herein by reference in its entirety.

EXAMPLE 1
Preparation of Dopamine Gluconamide and Dopamine Gluconamine

Representative compounds for use according to the instant methods were synthesized as disclosed in co-pending U.S. Patent Application Serial No. 09/547,506 (now U.S. Patent Serial No. 6,548,484 B1), incorporated herein by reference in its entirety. Briefly, gluconolactone and 3-hydroxytryamine were reacted slowly in methanol to form a white solid dopamine gluconamide precipitant. The product was collected by filtration, washing and drying *in vacuo* (i.e., dopamine gluconamide, Compound #1, below).

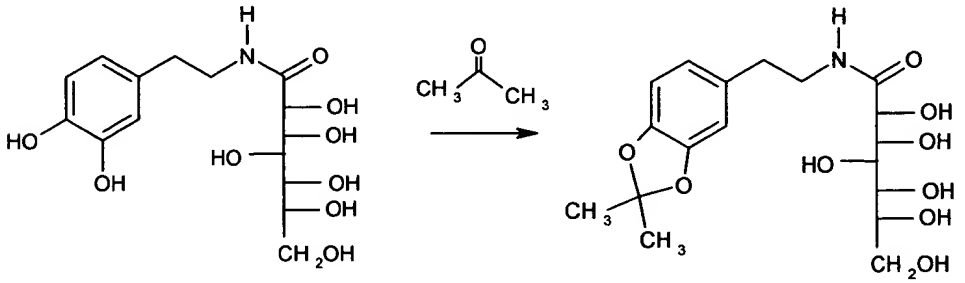
EXAMPLE 1-1
Preparation of Dopamine Gluconamide



Scheme 1

Gluconolactone (1.9 gm, 10.5 mmol) and triethylamine (TEA; 1.1 gm, 10.5 mmol) were added to methanol (25 mL) in a 100 mL round bottom flask with stirring. The gluconolactone was allowed to dissolve. When the solid was dissolved, the solution was stirred for an additional 10 minutes and then 3-hydroxytyramine (2.0 gm, 10.5 mmol) was added slowly, i.e., allowing it to dissolve. The reaction mixture was stirred in the dark for about 2 hrs. during which time a white solid precipitant appeared. The white solid precipitant was collected by filtration, washed with methanol (5 mL) and dried *in vacuo* for 6 hrs. to give dopamine gluconamide (1.69 gm, 5.10 mmol, 48.6% yield). Melting point of the synthesis product was 154-155°C. Predicted: $C_{14}H_{21}N_1$ (331.32): C -50.75%, H- 6.39%, N- 4.23%; analysis results of synthetic product: C, 50.65; H, 6.63; N, 4.44.

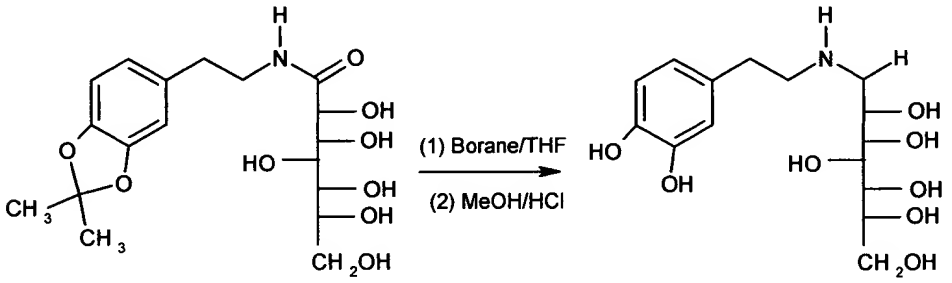
EXAMPLE 1-2
Protection of Aromatic Dopamine Hydroxyl Residues



Scheme 2

Dopamine gluconamide (EXAMPLE 1, supra; 0.75 gm, 2.26 mmol) was added to acetone (40 mL) in a 100 mL round bottom flask with stirring. Then, the reaction mixture was refluxed for 2 hrs., after which time it was allowed to cool to room temperature (about 22-25 C). The resultant white solid was removed by filtration and dried *in vacuo* for 7 hrs. yielding the isopropylidine protected dopamine gluconamide (0.68 gm, 1.83 mmol, 81.0% yield). Melting point of the synthesis product was 170°C.

EXAMPLE 1-3
Reduction of Isopropylidine Protected Dopamine Gluconamide



Scheme 3

Isopropylidene protected dopamine gluconamide (EXAMPLE 2, supra; 0.68 gm, 1.83 mmol) was slowly added to a 1 M Borane solution in THF (25 ml) in a 100 mL round bottom flask, with stirring. The reaction mixture was refluxed for 2 hrs. and then allowed to cool to room temperature. Excess solvent was removed by rotary evaporation. Methanolic HCl was added to the resultant residue and the solution refluxed for 2 hrs., after which time solvent was removed by evaporation and the solid recrystalized using a mixture of acetonitrile and ethanol. The recrystalized reduced dopamine gluconamide product was dried *in vacuo* for 6 hrs giving the dopamine gluconamine-HCl salt (0.22 gm, 0.62 mmol, 33.8% recovery). Melting point for the synthesis product was 151-152°C. Predicted $C_{14}H_{24}N_1$ (353.80); C, 47.53; H, 6.84; N, 3.96; Analysis result of synthesis product: C, 47.48; H, 6.93; N, 3.88.

EXAMPLE 1-4

Preparation of Dopamine Ribonamide

D-(+)-Ribonic acid gamma-lactone (2.0 gm, 13.5 mmol) was added to methanol (25 mL) in a 100 mL round bottom flask with stirring until dissolved, and then an additional 5 min. 3-Hydroxytyramine (2.6 gm, 13.5 mmol) was added slowly, allowing it to dissolve, with stirring, over the course of about 10 minutes. Triethylamine (1.4gm, 13.5 mmol) was then added and the reaction mixture refluxed for 4 hr. in the dark, during which time the solution acquired a slight yellow color. Solvents were removed by rotary evaporation using anhydrous ethanol as an azeotrope to remove any residual water. The resultant dried product constituted a thick syrup which solidified upon standing (1 hr.) to give a white solid. The white solid product was stirred (1 hr.) with acetone (40 mL), again resulting in a white solid as a product. The resultant solid was collected by filtration and dried *in vacuo* for 6 hrs. yielding dopamine ribonamide (3.83 gm, 12.7 mmol, 94.1% yield .) ^{1}H and ^{13}C-NMR results and CHN analyses were consistent with structure. Melting point was 90-91°C. Predicted $C_{13}H_{19}N_1$: (301.30): C, 51.82; H, 6.36; N, 4.65; Analysis results of synthesis product: C, 51.67; H, 6.40; N, 4.69.

EXAMPLE 1-5

Preparation of Dopamine Isopropylidine Ribonamide

Aromatic hydroxyl groups in dopamine ribonamide were protected by synthesizing the isopropylidine compound. Dopamine ribonamide (EXAMPLE 4; 1.0 gm, 3.32 mmol) was added to acetone (30 mL) in a 100 mL round bottom flask with stirring. The reaction mixture was refluxed for 5 hrs. and then allowed to cool to room temperature. The resultant white solid was collected by filtration and dried *in vacuo* for 7 hrs. to yield the isopropylidine protected dopamine ribonamide (0.99 g, 2.90 mmol, 87.6% yield). ^{1}H and ^{13}C-NMR results were consistent with structure. Melting point was found to 142-143°C.

EXAMPLE 1-6

Reduction of Isopropylidine Protected Dopamide Ribonamide
Yielding Dopamine Ribonamine

Isopropylidine-protected dopamide ribonamide (EXAMPLE 5; 0.70 gm; 2.05 mmol) was added slowly to 1 M Borane in THF (25 mL) in a 100 mL round bottom flask with stirring. The reaction mixture was refluxed for 2hr. and allowed to cool to room temperature. Excess solvent was removed by rotary evaporation and methanolic HCl was added to the resulting residue. The resuspended residue was refluxed for 2 hr. and solvent was then evaporated yielding a thick hygroscopic syrup (complicating melting point analysis). The syrup was dried *in vacuo* for 6 hrs. to give the dopamine ribonamine-HCl salt as product (0.20 gm., 0.62 mmol, 30.3% yield.) ^{1}H and ^{13}C-NMR results were consistent with structure.